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ORIGINAL WORK

What Do We Do When the ICP Goes Up?

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Abstract

Background/Objective: We sought to study which intracranial pressure (ICP)-lowering treatments are actually administered following the diagnosis of a clinical intracranial hypertension episode (CLICHÉ) during modern, routine care.

Methods: We performed a secondary analysis of data from patients with ICP only (normal or blinded partial pressure of brain tissue oxygen [$PbtO_2$]) in the Brain Tissue Oxygen Monitoring and Management in Severe Traumatic Brain Injury (BOOST II) randomized trial. We identified "minimalist" (*forme fruste*) CLICHÉs (defined by 5 min of ICP > 20 lasting ≤ 60 min, requiring only Tier One treatments) and catalogued all interventions by frequency, grouping and distribution of administration. Tier One treatments were not rank-ordered.

Results: Of the 119 randomized patients, 70 had 509 CLICHÉs that met *forme fruste* definition with complete datasets (71% of total CLICHÉs). Analgosedation adjustment and cerebrospinal fluid (CSF) drainage were the predominant treatments, used respectively in 72% and 33% of full CLICHÉs and within the first 15 min in 53% and 31%. In combination, they were the third most common intervention. Treatments often involved agent combinations (41% for full CLICHÉs; 46% within the first 15 min). Treatments that could be readily and discretionally administered by the bedside clinician represented 76% of treatments for full CLICHÉs and 69% for early interventions.

Conclusions: Analgosedation adjustment predominates as the treatment of choice for *forme fruste* CLICHÉs despite scarce literature support regarding mechanism, efficacy or influence on outcome. Frequent use of agent combinations confounds use of treatments (e.g. therapeutic intensity level) as a descriptive variable. Although details regarding clinical reasoning underlying intervention choices are lacking, it appears that intervention choice may be influenced by expediency outside of effectiveness. These findings accent the importance of understanding how treatment protocols are actually implemented. Investigation of the proper role of analgosedation adjustment and treatment combinations in ICP control is needed. Current management practices require targeted, physiology-based treatment guidance.

Keywords: Traumatic brain injury, Intracranial pressure, Monitoring, Clinical protocols, Therapeutics, Critical care, Hypnotics and sedatives

Introduction

Intracranial pressure (ICP) is strongly associated with outcome from severe traumatic brain injury (TBI) [1, 2]. Analysis of the influence of intracranial hypertension, however, is confounded by the effects of ICP-lowering therapies once the pressure has exceeded a perceived threshold. This obscures the role of ICP as a simple endpoint. In response, the therapeutic intensity level (TIL) was conceptualized by Professor Lawrence Marshall and operationalized by Maset et al. [3] as a measure of management magnitude, an index of the resistance of ICP to intervention and a variable in outcome prediction models [4–6]. It is characterized by listing individual intracranial

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hypertension interventions, with or without clustering, generally with weights assigned to each treatment [3, 7]. Interventions are assessed and summed periodically (e.g. hourly, daily). The interagency common data elements version has been validated specifically as a tool to quantify ICP treatment (vs. a TBI severity descriptor), an outcome measure, etc.

Various algorithms have been developed to guide ICP treatment, either sequential [8] or grouped in non-rank-ordered fashion into tiers [9–11]. A guiding principle in such algorithms is ranking treatments on the basis of risk:benefit ratio. Ergo, sedation, analgesia, head-of-bed (HOB) elevation, temperature manipulation, maintenance of cerebral perfusion pressure (CPP) and cerebrospinal fluid (CSF) drainage (if an external ventricular drain [EVD] is available) have been grouped as first options. Although such is considered the safest approach, the burgeoning goal of precision medicine via therapy targeted at specific underlying pathophysiologic abnormalities is not directly addressed. The grouping of multiple options within a tier allows targeting, but choice of treatment remains undirected and is left to the treating clinician.

To bolster the value of the algorithm-independent TIL in describing methods of treating intracranial hypertension, we have investigated the patterns of individual interventions used in treating individual clinical intracranial hypertension episodes (CLICHÉs). We studied data from the ICP-only (normal or blinded partial pressure of brain tissue oxygen [$PbtO_2$]) cohorts of the Brain Tissue Oxygen Monitoring and Management in Severe Traumatic Brain Injury (BOOST II) randomized trial in which treatment of CLICHÉs was protocolized in a manner comparable to evidence-based, routine practice.

Materials and Methods

BOOST II (ClinicalTrials.gov: 00974259) was a phase II randomized controlled trial investigating the safety and efficacy of supplementing ICP-monitor-based TBI care with $PbtO_2$-monitor-based treatment in decreasing the incidence and magnitude of low cerebral oxygenation values [12, 13]. All patients received both ICP and $PbtO_2$ monitors, the output of which was collected continuously by digital recorders (Moberg ICU Solutions, Ambler, PA) and averaged over 1-min intervals for this analysis. ICP data from all patients were recorded and displayed for use in routine care. Patients in the ICP-only arm had their $PbtO_2$ results recorded, but these were blinded to the clinicians.

We adopted the CLICHÉ definitions from the BOOST II manual of procedures (MOP), which defined a treatable insult as a "5 min continuous ICP elevation $\geq$ 20 mm Hg (not due to iatrogenic or reversible maneuver)" as identified by the bedside clinician (BC) whereupon "intervention must be initiated within 15 min of an event becoming treatable" (Fig. 1). Identification of onset and ending of CLICHÉs was clinical, according to the BC's interpretation of data from the monitor (as recorded on study case report forms), not from the Moberg device.

CLICHÉs were addressed using tier-based treatments based on Brain Trauma Foundation Guidelines [14] and Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC) recommendations [9, 11] (Electronic Supplementary Materials [ESM] Tables 1S and 2S). Critical to the present study, there was no treatment rank-order within a tier, allowing ad hoc choice of interventions at the discretion of the clinician. The study confirmed that $PbtO_2$-guided-therapy lowered cerebral desaturation duration and magnitude [13].

For the current study, we limited our investigation to *forme fruste* (minimalist) CLICHÉs, defined as episodes of isolated intracranial hypertension but normal or blinded $PbtO_2$, lasting $\leq$ 60 min and necessitating only minimal (Tier One) treatment, as delimited in the BOOST II protocol (https://links.lww.com/CCM/C763) 12 (Table 1).

For the purpose of exploring a possible role for expediency in guiding the choice of treatments, we grouped interventions that are generally readily available to the BC and immediately subject to discretionary administration. This collection included analgosedation adjustment, CSF drainage, adjustment of body temperature to < 38 °C and manipulating the head of the bed (HOB). We did not include mannitol and hypertonic saline administration in this group, as they generally require a situationally specific order (and, occasionally, delivery to the bedside) or adjustment of the minute ventilation, as this most frequently involves a respiratory therapist with or without an order.

The data were abstracted directly from the BOOST II dataset, facilitated by one of the authors (J.B.) having developed and maintained the database for the study. The upset plots were done by hand in PowerPoint (Microsoft, Redmond, WA). As this is a descriptive study and the analyses are simple arithmetic calculations, no statistical software package was used.

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Results

Of the 119 randomized patients, 82 had 737 CLICHÉs. Of these, 70 patients with complete (Moberg) datasets

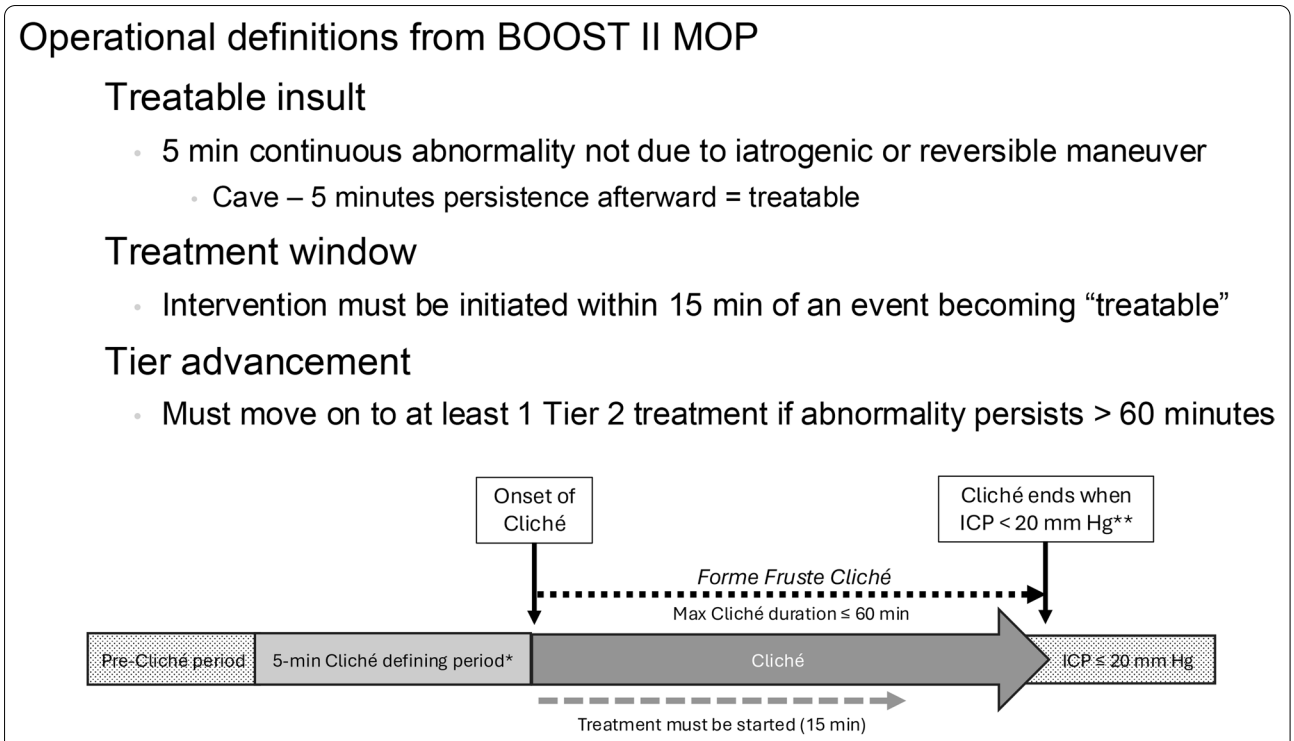
Operational definitions from BOOST II MOP
Treatable insult
5 min continuous abnormality not due to iatrogenic or reversible maneuver
Cave – 5 minutes persistence afterward = treatable
Treatment window
Intervention must be initiated within 15 min of an event becoming "treatable"
Tier advancement
Must move on to at least 1 Tier 2 treatment if abnormality persists > 60 minutes
Onset of Cliché
Cliché ends when ICP < 20 mm Hg**
Forme Fruste Cliché
Max Cliché duration ≤ 60 min
Pre-Cliché period
5-min Cliché defining period*
Cliché
ICP ≤ 20 mm Hg
Treatment must be started (15 min)
*MOP definition: 5 minutes continuous abnormality not due to iatrogenic or reversible maneuver.
** ICP must remain < 20 mm Hg for 20 min to begin a new Cliché

Fig. 1 Diagrammatic representation of the definitions from the BOOST II MOP used in this study. A 5-min period of sustained intracranial hypertension as documented by the bedside clinician on the basis of observations from the ICP monitor defined a treatable insult and was the initiating incident for each CLICHÉ. *Forme fruste* CLICHÉs were periods of intracranial hypertension recorded by the bedside clinician, limited to ≤ 60 min and ending when the bedside clinician documented that the ICP returned to < 20 mm Hg

Table 1 Tier One treatments used in Scenario B (intracranial hypertension in patients randomized to ICP-monitoring-only (blinded PbtO2 monitor values)*

Adjust head of bed to lower ICP.
Ensure temperature is < 38 °C.
Adjust pharmacologic analgesia and sedation: titrate to effect. Propofol and/or benzodiazepines should be used for sedation, and fentanyl as analgesic.
CSF drainage (if EVD available). Titrate to effect.
Either continuous or intermittent CSF drainage allowed per site protocol.
Standard dose mannitol (0.25–1.0 g/kg) to be administered as bolus infusion. Titrate to ICP, control and maintain serum osmolality < 320 mOsm or gap < 20.
Hypertonic saline. Can be administered as either bolus or continuous infusion (latter at 3% NaCl at dose of 0.5–1 mL/kg). Titrate to ICP control and maintain serum Na^+ 155–160).
Adjust ventilator to maintain $paCO_2$) 35–40 mm Hg.

* There is no rank ordering of the individual treatments within a tier. Choice of treatments and order of their use is at the discretion of the managing clinician. $PaCO_2$, partial pressure of carbon dioxide in arterial blood

had a total of 720 CLICHÉs, 509 (71%) of which met our *forme fruste* definition by being isolated intracranial hypertension (i.e. normal or blinded $PbtO_2$), being ≤ 60 min in total duration and receiving only Tier One treatments. Patient demographics are illustrated in ESM Table 3S.

Figure 2 is an upset plot of treatments delivered for CLICHÉs at any time within the 60 min. It includes all Tier One treatments. The predominant individual treatment was analgosedation adjustment. It was used in 72% of CLICHÉs—in isolation in 39%. CSF drainage was used in 33% of CLICHÉs, in isolation in only

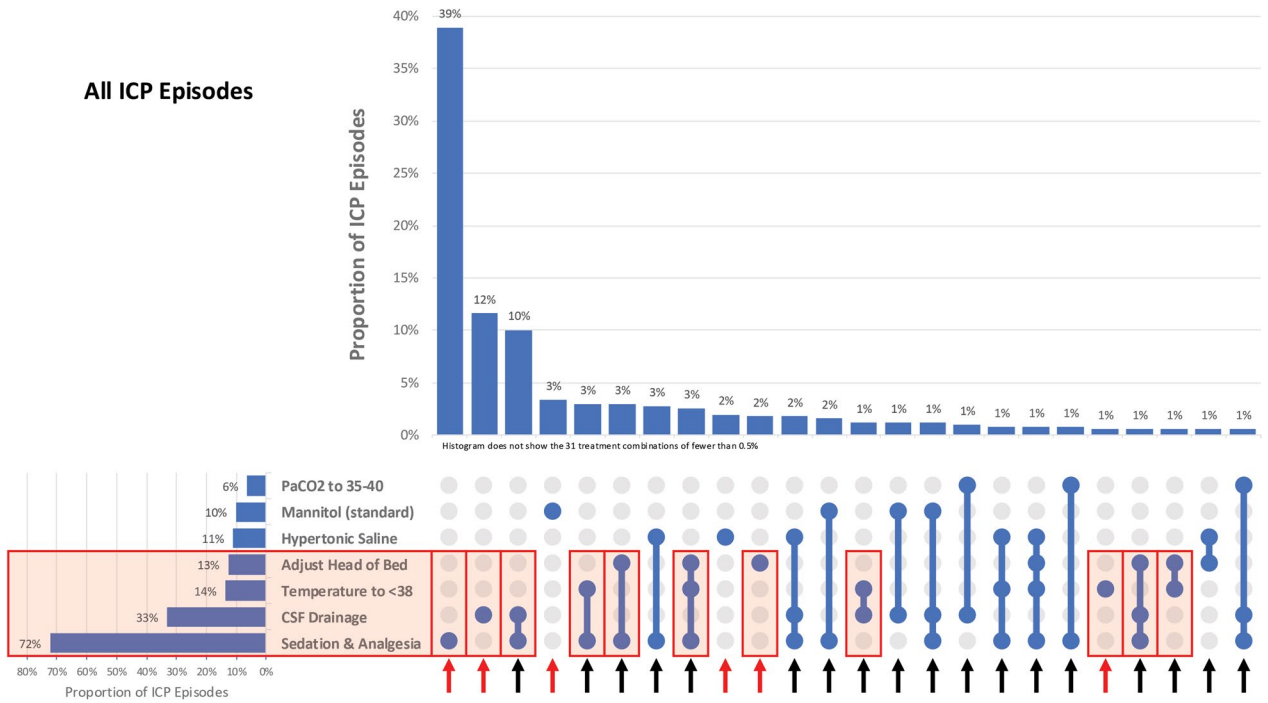

Fig. 2 Upset plot of the distribution of individual and combinations of therapeutic interventions for episodes of isolated intracranial hypertension but normal or blinded $PbtO_2$ lasting ≤ 60 min and necessitating only minimal treatment, defined as Tier One treatments as delimited in the BOOST II protocol [13]. The proportions indexed on the ordinate axis represent the treatments or combinations thereof as listed directly beneath the bars. The horizontal bars in the lower left represent the proportion of intracranial hypertension episodes treated with the individual interventions listed. Tinted boxes include treatments "ready-to-hand" for the bedside clinician, generally not requiring a CLICHÉ-specific order. Red arrows indicate individual treatments; black arrows indicate combination treatments

12%. The combination of analgosedation adjustment with CSF drainage was used in 10% of CLICHÉs. The remaining combinations were used in less than 15% of CLICHÉs.

We examined situational "first choice" treatments by investigating the subset of interventions employed during the first 15 min of each CLICHÉ (Fig. 3). As shown in the inset figure, the distributions are very comparable, with analgosedation adjustment being predominant (53% of CLICHÉs) and CSF drainage being second (31% of CLICHÉs). The combination of analgosedation adjustment with CSF drainage was again the third most common (30% of CLICHÉs) but of a relatively lower frequency than that shown for the entire CLICHÉ duration (Fig. 2). The frequency of the distribution of these early treatments is shown in Table 2.

Of the 24, 6 (25%) treatment choices for full CLICHÉs involved single agents vs. combinations (red vs. blue arrows in Fig. 2). In terms of total treatments, 59% were single-agent interventions. During the first 15 min, 7 of the 23 (30%) choices were for a single agent (red vs. blue arrows in Fig. 3), representing 54% of all treatments administered. Therefore, two or more simultaneous interventions were selected for nearly half of these *forme fruste* CLICHÉs.

CSF drainage is the second most frequent intervention and is limited to CLICHÉs where an EVD is available. We developed a separate upset plot for the 214 CLICHÉs occurring in the 23 patients with EVDs (Fig. 4). CSF drainage is the treatment of choice when an EVD is present, although the proportion of CLICHÉs in which analgosedation adjustment is used (60%) is similar to CSF drainage (71%).

We recognize that the choice of individual treatments may be influenced by baseline systemic factors (e.g. hyperventilation, hyperosmolar treatment and antipyrexia by pre-existing hypocarbia, hyperosmolality or normothermia respectively). Unfortunately, the BOOST II database lacks sufficient granularity to address such confounding in detail. As a first approximation, we analysed treatment choices for first-time CLICHÉs (all and EVD-only), as such should represent instances with minimal confounding (Fig. 5). For all first-time CLICHÉs, analgosedation adjustment remained the strongly predominant choice, and the four most popular interventions all fall into our expedient category. For first-time EVD-only

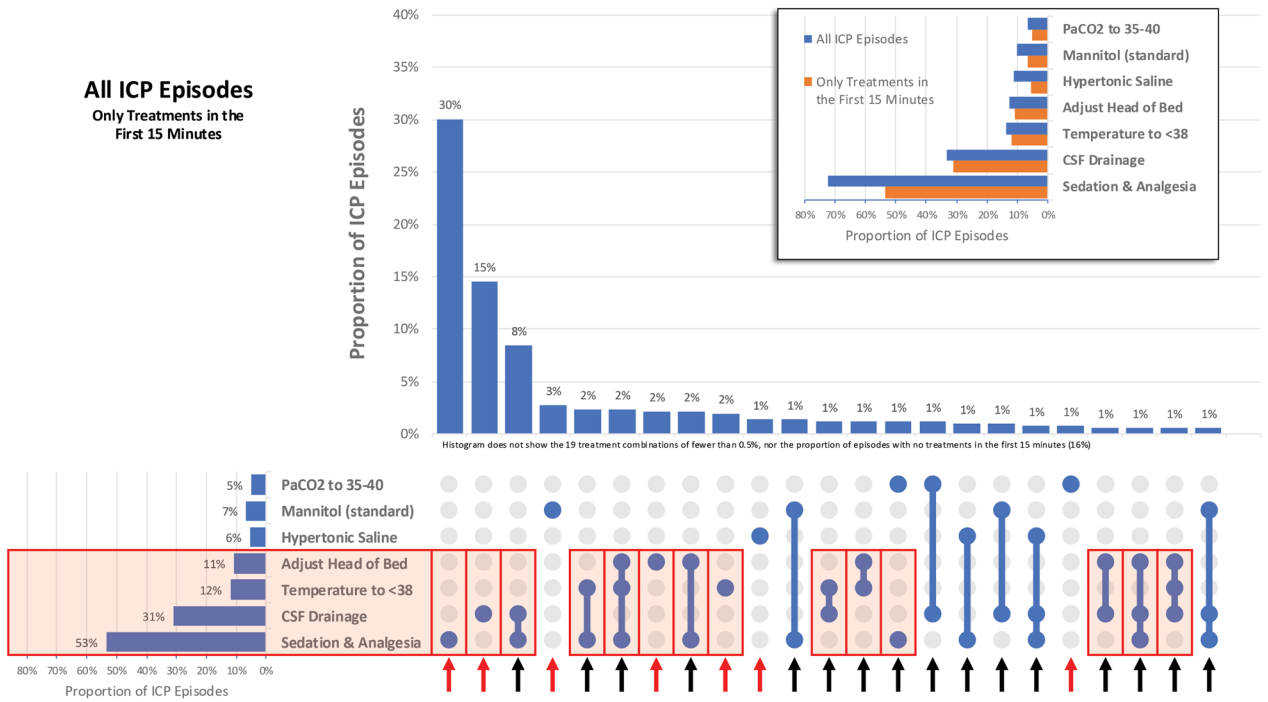

Fig. 3 Upset plot of the distribution of individual and combinations of therapeutic interventions for episodes of isolated intracranial hypertension but normal or blinded $PbtO_2$ lasting ≤ 60 min and necessitating only minimal treatment, defined as Tier One treatments as delimited in the BOOST II protocol [13]. This figure includes only "early" treatments (within 15 min of the CLICHÉs being recognized according to the BOOST II protocol). The proportions indexed on the ordinate axis represent the treatments or combinations thereof as listed directly beneath the bars. The horizontal bars in the lower left represent the proportion of intracranial hypertension episodes treated with the individual interventions listed. Tinted boxes include treatments "ready-to-hand" for the bedside clinician, generally not requiring a CLICHÉ-specific order. Red arrows indicate individual treatments; black arrows indicate combination treatments. The embedded diagram compares the proportion of ICP episodes receiving individual Tier One treatments for entire CLICHÉs and the first 15 min of each CLICHÉ

CLICHÉs, analgosedation adjustment was also the first choice, in contrast to CSF drainage being first when all EVD CLICHÉs are examined (Fig. 4).

Even for first-time CLICHÉs, combinations of agents were common (red arrows in Fig. 4)—44% for all such episodes and 35% for EVD-only cases.

To analyse expediency as a possible co-variable in treatment choices, we grouped treatments we considered to be generally readily available to the BC and immediately subject them to discretionary administration. These are highlighted in Figs. 2 and 3 by tinted boxes. The size of this subpopulation and the fact that is contained the treatments with the highest usage frequency are notable. For all CLICHÉs, 76% of all treatments are solely within this group as are 69% of all treatments given during the first 15 min.

Understanding the physiologic response to analgosedation adjustment administrations for intracranial hypertension would be valuable in assessing its appropriateness. Unfortunately, BOOST II lacks sufficient data for such assessment. Although this study is focused on *forme fruste* CLICHÉs, the baseline ICP defining the episode might influence the indication for and response to analgosedation adjustment. As a limited view of this question, we examined the correlation between two baseline BC-recorded ICP ranges (≥ 20–< 30 mm Hg [$N = 167$] vs. ≥ 30 mm Hg [$N = 31$]) and the subsequent electronic ICP response to treatment (Fig. 1S). This revealed adequate response (ICP < 20 mm Hg) at > 10–60 min following analgosedation adjustment for both ranges, without notable differences. Such responses would appear satisfactory to the BC over the short term.

It is possible for ICP lowering to have a deleterious effect if it is obtained through a decrease in CPP, depending on the degree of CPP lowering, the status of pressure autoregulation and the shape of the autoregulation curve. While we lack sufficient data to address such possible untoward effects in detail, we have examined the influence of analgosedation adjustment on subsequent average CPP levels and not found evidence of undesired depression (Fig. 2S). As we lack evidence on concomitant pressor use, which is a common response to a drop in CPP of any aetiology, this analysis is incomplete.

Table 2 Frequency of the distribution of treatments administered during full CLICHÉS and during the first 15 minutes of individual CLICHÉS

	All Txs	Tx in the first 15 min
ICP episodes	509	509
$PaCO_2$ to 35–40		
No	476 (94%)	483 (95%)
Yes	33 (6%)	26 (5%)
$PaCO_2$ to 35–40 only	2 (0%)	4 (1%)
With other Txs	31 (6%)	22 (4%)
Mannitol		
No	457 (90%)	475 (93%)
Yes	52 (10%)	34 (7%)
Mannitol only	17 (3%)	14 (3%)
With other Txs	35 (7%)	20 (4%)
Hypertonic saline		
No	452 (89%)	481 (94%)
Yes	57 (11%)	28 (6%)
Hypertonic saline only	10 (2%)	7 (1%)
With other Txs	47 (9%)	21 (4%)
Adjust HOB		
No	444 (87%)	454 (89%)
Yes	65 (13%)	55 (11%)
Adjust HOB only	9 (2%)	11 (2%)
With other Txs	56 (11%)	44 (9%)
Temperature to < 38		
No	439 (86%)	448 (88%)
Yes	70 (14%)	61 (12%)
Temperature to < 38 only	3 (1%)	10 (2%)
With other Txs	67 (13%)	51 (10%)
CSF drainage		
No	340 (67%)	351 (69%)
Yes	169 (33%)	158 (31%)
CSF drainage only	59 (12%)	74 (15%)
With other Txs	110 (22%)	84 (17%)
Sedation/analgesia		
No	141 (28%)	237 (47%)
Yes	368 (72%)	272 (53%)
Sedation/analgesia only	198 (39%)	153 (30%)
With only CSF	51 (10%)	43 (8%)
With non-CSF Txs	56 (11%)	41 (8%)
Other Tx combo	63 (12%)	35 (7%)

HOB, head of bed; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; Tx, treatment

Discussion

Clinical TBI research commonly focuses on the relations between successful ICP control and outcome, the efficacy of ICP monitoring in that effort, the role of individual intercessions in decreasing the ICP burden to improve recovery, and the place of more dramatic interventions (e.g. decompressive craniectomy, hypothermia) in salvaging refractory cases. Laboratory research generally focuses on pathophysiological mechanisms and potential therapeutic pathways. However, the pragmatic middle ground wherein evidence/guidelines/recommendations are applied to CLICHÉs is poorly understood. We have used the BOOST II database to explore the actual BC-directed distribution of interventions as it is a published, high-quality study conducted as a prospective, randomized trial with prespecified treatment protocols based on routine clinical practice and high-resolution data collection undertaken at experienced neurotrauma centres under central monitoring committee oversight. Management was consistent with widely accepted recommendations [9, 11, 15, 16], and the study intervention ($PbtO_2$ monitoring) was blinded in our study cohort. We therefore suspect that our data generally represent TBI care patterns of the majority of trauma centres in the USA and probably most global high-resource settings as well. In this study, we have asked: "what is done when the ICP goes up?" While ICP management was protocolized in BOOST II, treatment choice within a given tier was at the medical team's discretion. Specifically, there was no rank ordering of treatments within a tier. Here, we describe the treatments administered by the BC treating patients with relatively modest (*forme fruste*) CLICHÉs, which represent 71% of all intracranial hypertension episodes in this dataset.

Everyone who manages TBI has received calls such as "I've maxed out the propofol and fentanyl, the HOB is at 45°, and the EVD doesn't drain anymore. The noradrenaline infusion is high to keep CPP above 60. What should I do?" The fundamental question is, of course, why the ICP is elevated. However, also important is why several of the available Tier One treatments have been selectively maximized, whether those have been the optimal choices for this patient and how to address the high-dose pressors required to manage the side effects of the current treatment regimen.

The most notable treatment distribution facet is the predominance of analgosedation adjustment as a primary response. Frequently applied early in a CLICHÉ (first 15 min), it continues to be used for the entire course of Tier One treatment. Acute associations between such treatment and decreased ICP are commonly observed. Untreated agitation and pain can contribute to high ICP, so there is a rational basis for the use of sedatives and analgesics in this setting. Some sedatives, such as propofol, are also thought to reduce ICP via suppressive effects on cerebral metabolic rate of oxygen ($CMRO_2$) and cerebral blood flow (up to the limits of metabolic autoregulation) [17]. Despite this theoretical basis, clinical literature is sparse regarding understanding the

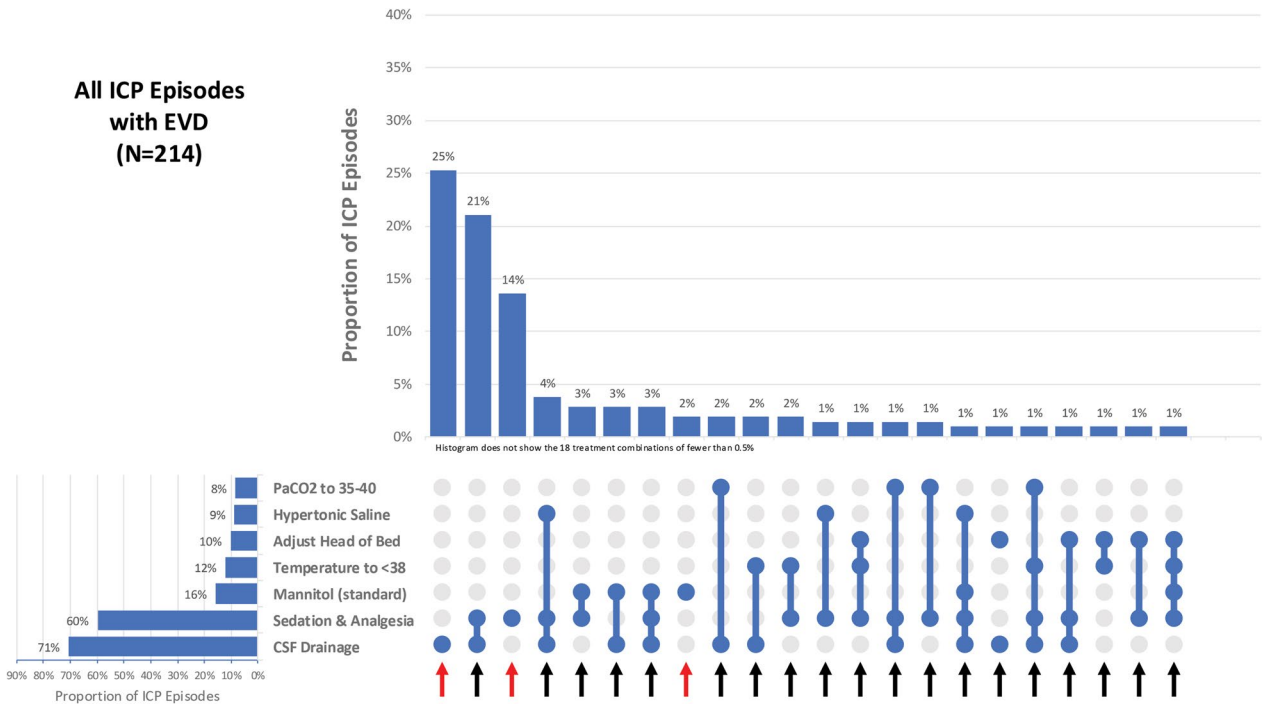

Fig. 4 Upset plot of the distribution of individual and combinations of therapeutic interventions in patients with EVDs for episodes of isolated intracranial hypertension but normal or blinded $PbtO_2$ lasting ≤ 60 min and necessitating only minimal treatment, defined as Tier One treatments as delimited in the BOOST II protocol [13]. The proportions indexed on the ordinate axis represent the treatments or combinations thereof as listed directly beneath the bars. The horizontal bars in the lower left represent the proportion of intracranial hypertension episodes treated with the individual interventions listed. Red arrows indicate individual treatments; black arrows indicate combination treatments

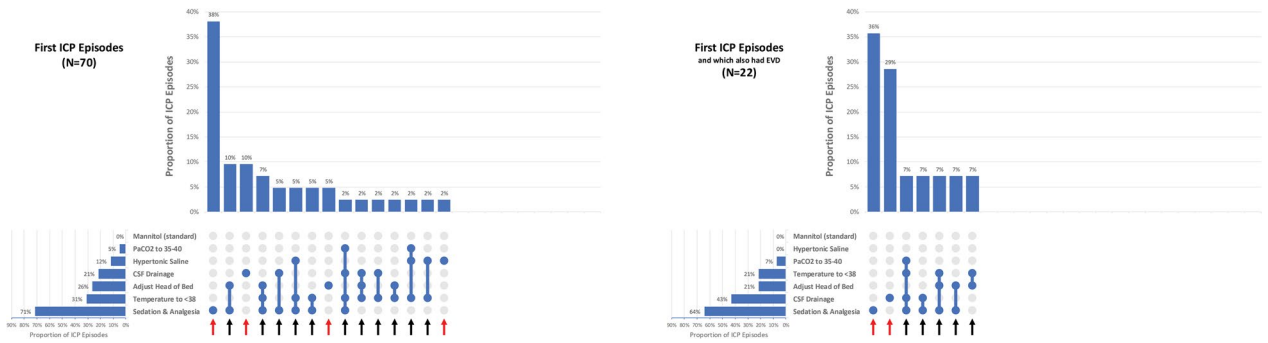

Fig. 5 Upset plot of the distribution of individual and combinations of therapeutic interventions for first-time episodes of isolated intracranial hypertension but normal or blinded $PbtO_2$ lasting ≤ 60 min and necessitating only minimal treatment, defined as Tier One treatments as delimited in the BOOST II protocol [13]. The left plot represents all first-time episodes. The right plot represents first-time episodes in patients monitored with an EVD. The proportions indexed on the ordinate axis represent the treatments or combinations thereof as listed directly beneath the bars. The horizontal bars in the lower left represent the proportion of intracranial hypertension episodes treated with the individual interventions listed. Red arrows indicate individual treatments; black arrows indicate combination treatments

mechanics of analgosedation adjustment effects such as influence on compliance, duration of effect, relationship to underlying CLICHÉ pathophysiology and interactions with other treatment modalities. The most recent edition of the Brain Trauma Foundation (BTF) adult TBI guidelines [15, 16] in addressing the question "does the use of sedatives improve outcomes?" (excluding barbiturate coma) found that Class 2 evidence was limited to a single, comparatively small study comparing propofol with morphine [18]. The BTF limited their

recommendations on anaesthetics, analgesics and sedatives to one Level IIB statement of "Although propofol is recommended for the control of ICP, it is not recommended for improvement in mortality or 6-month outcomes. Caution is required as high-dose propofol can produce significant morbidity". A recent scoping review of the use of sedatives (propofol, ketamine, benzodiazepines, opioids and alpha-2 agonists) in the treatment of moderate-to-severe TBI focused on the primary outcome of ICP control concluded that "there is a paucity of high-quality evidence to inform the optimal use of analgosedative agents in the management of m-sTBI, inferring significant scope for further research" [19]. Based on the apparent predominance of analgosedation adjustment in treating the most basic instances of intracranial hypertension, much more investigation is needed into the efficacy, mechanisms of action, toxicity and interactions with other agents of these commonly used drugs, given the magnitude of exposure to analgosedation adjustment in TBI patients. In BOOST-2, analgosedation adjustment was used in the vast majority of *forme fruste* CLICHÉs; is this the correct approach, or should these agents be used in a more targeted fashion, depending on the pathophysiology of intracranial hypertension in individual patients, perhaps modified by sedation scaling?

Examination of the distribution of treatments reveals that the only interventions that reach over 25% of CLICHÉs (alone or in combination) are analgosedation adjustment and CSF drainage, with the relative frequency of the latter being limited by the prevalence of EVDs in the study population (see below). As a direct intracranial volume manipulation, it is prioritized in current treatment regimens when a drain is in place and consideration of EVD implantation is recommended when one is not primarily used for ICP monitoring. The use of other Tier One interventions vary between 5% and 12% for the initial 15 min and 6% and 14% for full CLICHÉs. The administration of hyperosmolar solutions appear more delayed in their distributions. Examining the combination of early-applied interventions and the overall frequency of analgosedation adjustment as a treatment suggested an unanticipated potential factor determining the distribution and timing of treatment choices. It also illustrates a shortcoming in the TIL, which does not account for frequency and distribution factors in calculating the TIL value [20, 21].

Characteristically, the BC makes the determination that ongoing ICP elevations have reached the treatment threshold. In BOOST II, treatable was defined as "a 5 min continuous ICP elevation $\geq$ 20 mm Hg (not due to iatrogenic or reversible maneuver)". CLICHÉ treatment was mandated as follows: "intervention must be initiated within 15 min of an event becoming treatable". The BC also has the goal of avoiding or minimizing the incidence of CLICHÉs and the responsibility of delivering treatments. Frequently, standing orders allow the BC discretion to independently initiate or titrate certain treatments. From the Tier One menu, these would generally include analgosedation adjustment, CSF drainage, temperature manipulation and alteration of the HOB height. Other treatments, such as hyperosmotics or ventilator adjustment, would generally require obtaining an order and, perhaps, briefly awaiting arrival of the agent or respiratory therapist to the bedside. These "ready-to-hand" treatments, alone or in combination, are highlighted in Figs. 2 and 3, which illustrate that 69% of interventions during the early CLICHÉ period and 76% of interventions during the entire CLICHÉ fall into this category of expedient manoeuvrers. Disproportionate analgosedation adjustment choice in first-time episodes, where treatment choice should be minimally biased, even when an EVD was present (Fig. 5), and far outstripping use of common and well-supported agents such as hypertonic saline and mannitol, further supports the influence of an extraneous factor in intervention selection. Obviously, these treatments represent the majority (57%) of the available Tier One options which would clearly create bias towards their selection if all were considered equal. However, considering the various methods of action of these agents and their different targeted physiological abnormalities, we do not believe that their expediency warrants consideration as a factor in their apportionment. On the basis of these observations, we suspect that the choice of interventions is notably influenced by non-physiologically based factors not considered when designing treatment algorithms [9, 11]. Organizing treatments into hierarchical tiers accents safety and supports physician choice while providing structured management. Unfortunately, it does not inherently provide guidance to aid such choices. Outside of emergencies, expediency should not be a guiding principle.

Analgosedation adjustment use might be influenced by sedation indices (e.g. Richmond Agitation-Sedation Scale [RASS], Bispectral Index [BIS]), although these were not mandated for BOOST II and it is our clinical impression that analgosedation adjustment use for acute CLICHÉs is rarely influenced by level of sedation even now. Our distributions should therefore be viewed as approximations, although we do not believe that this will invalidate the relevancy of the disproportionate incidence of analgosedation adjustment use. As EVD presence was recorded and is required for CSF drainage, we were able to separately examine the subset of CLICHÉs wherein CSF drainage was uniquely an option. This did alter the relative distribution of interventions—CSF drainage moving to first choice—but analgosedation adjustment use remained a

very close second. Additionally, for first-time CLICHÉs where an EVD was available, analgosedation adjustment was the most common intervention. These proportions may be understated, as continuous drainage (vs. "burping") would not be recorded as an acute intervention and CSF drainage might not be chosen when the EVD drains poorly. Mechanistically, it is easily understandable why CSF drainage should be the first choice when an EVD is available. That analgosedation adjustment use was such a close second in these patients we believe further reinforces its apparently favourable status as an overall treatment choice.

The third point here is the apparent frequency of initiating treatment of CLICHÉs using a combination of agents. This questions consideration of the TIL as a measure of the resistance to treatment of CLICHÉs, since it is likely that the choice of uni- or multi-agent treatment is influenced by practice patterns or individual preferences outside of pure ICP refractoriness. Elevated TIL values due to non-pathophysiology-based use of multiple agents will confound the TIL's value as an index of resistance of ICP to treatment. Weighting all treatments individually will not account for such influences, perhaps supporting consideration of weighted handling of combinations in calculating the TIL.

Initiating the treatment of CLICHÉs with multiple concomitant agents will also likely increase the apparent impact on the ICP value. In a crisis-based management scheme, where treatment is predicated on the occurrence of intracranial hypertension with achieving any subthreshold ICP constituting success, this will confound our understanding of the effectiveness of treatment. It is likely that concomitantly monitoring important underlying physiologic parameters (e.g. cerebral compliance or perfusion-metabolism matching) might help direct (and, perhaps, limit) treatment intensity beyond simple threshold effects. An alternative would be a tranquillity approach, focusing on avoiding CLICHÉs once a tendency towards intracranial hypertension has been established [22, 23]. This is one potential lesson to be gleaned from studies of the management of suspected intracranial hypertension in the absence of monitoring, where treatment titration is a basic principle. Similar outcomes between monitored and un-monitored severe TBI (sTBI) cohorts may also reflect differences in underlying treatment philosophy [24, 25].

Following decades of interventions being applied to lower ICP, our simple inspection of actual practices has revealed several conundrums needing consideration. The predominance of analgosedation adjustment as the primary intervention is at odds with the dearth of research in support of its overall efficacy, mechanisms of action of individual agents and relative value vs. alternate agents. We are not suggesting that such use of analgosedation is inappropriate. This study could not capture the bedside reasoning of the clinicians, or their rationale for choosing these treatments first. However, given the apparent degree to which TBI patients are exposed to CLICHÉ-related analgosedative adjustments, evidentiary justification and usage guidelines are indicated. The influence of factors other than physiologic targeting in the choice of treatments also warrants recognition and possible adjustment. Finally, the apparent tendency to address CLICHÉs with multiple simultaneous agents vs. select individual interventions, with a focus primarily on number-lowering, raises questions about the design of the TIL as an operational variable and the crisis-based philosophy generally applied to intracranial hypertension management. The application of our overall scientific and clinical knowledge of sTBI in terms of successfully treating intracranial hypertension appears to want improved understanding of how the rubber hits the road.

The major limitation of this investigation is that it relies on a single study not designed to examine this question. Although BOOST II was of very high quality, included ten sites and their protocolized treatment approach parallels modern management strategies, much relevant data are missing. We cannot examine the relative applicability of all Tier One treatment for each CLICHÉ, so our distributions must be considered approximations. Generalization of our findings obviously requires corroboration from datasets produced in other settings under other conditions. However, the demonstrated value of empirically studying actual practice patterns, a major contribution of this study, is independent of this limitation. We have also only examined the simplest (*forme fruste*) CLICHÉs and our observed correlations may not apply to more complex or protracted episodes. Being by far the most predominant form of CLICHÉ, however, the potential benefit of improved understanding of the risk:benefit balance of such treatment has independent value.

Supplementary Information

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Author Contribution
Randall M. Chesnut: conceptualization methodology, formal analysis and writing – original draft. Robert H. Bonow: methodology, methodology, formal analysis and writing – review and editing. Nancy Temkin PhD: methodology, formal analysis and writing – review and editing. Jason Barber: data curation, formal analysis and writing – review and editing. Christine Park: methodology, formal analysis and writing – review and editing. This study used the data from the Brain Tissue Oxygen Monitoring and Management in Severe Traumatic Brain Injury (BOOST II randomized control trial [RCT] under the conditions of the BOOST II data use agreement. No formal institutional review board (IRB) approval was needed for this work.

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